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Liver Digest

A weekly update of PLRC happenings

February 6, 2020

PITTSBURGH LIVER RESEARCH CENTER

A partnership of University of Pittsburgh & UPMC

www.livercenter.pitt.edu

Featured Faculty - Dr. David Geller

Please remember to acknowledge support from the PLRC (NIH/NIDDK P30DK120531) in your publications and presentations.

In this issue

Liver Seminars

Pediatric Gastroenterology, Hepatology, and Nutrition Lecture Series

Fri., 2/7/2020

8:00 - 9:00 am

UPMC Children's Hospital of Pittsburgh Plaza Building Conference Room #307

Kareem Abu-Elmagd, MD, PhD

Director, Gut Rehabilitation & Transplant

Cleveland Clinic

"Autologous Gut Reconstruction in the New Era of Intestinal and Multivisceral Transplantation"

Aging Institute Seminar

Thurs., 3/12/2020
4:00-5:00 pm
S100A BST

Joseph S. Takahashi, PhD
Professor and Chair, Department of Neuroscience
Investigator, Howard Hughes Medical Institute
Lloyd B. Sands, Distinguished Chair in Neuroscience
Peter O'Donnell Jr. Brain Institute
University of Texas Southwestern Medical Center

"Circadian Clocks and the Importance of Timing in Aging and Longevity"
Although trained as a neuroscientist, Dr. Takahashi's recent work has shifted to understanding the interplay among circadian clock, metabolism and aging in the metabolic tissues including liver.

Informal reception to follow at 5:00-6:00 p.m.

The full schedule of Enrichment activities is posted on **https://www.livercenter.pitt.edu/events**.

Faculty Highlights

PLRC members collaborating on manuscripts are noted in red.

Original Article:
Shuster DL, Shireman LM, Ma X, Shen DD, Flood Nichols SK, Ahmed MS, Clark S, Caritis S, **Venkataramanan R**, Haas DM, Quinney SK, Haneline LS, Tita AT, Manuck TA, Thummel KE, Brown LM, Ren Z, Brown Z, Easterling TR, Hebert MF. Pharmacodynamics of glyburide, metformin

and glyburide/metformin combination therapy in the treatment of gestational diabetes mellitus. Clin Pharmacol Ther. 2019 Dec 23. doi: 10.1002/cpt.1749. PubMed PMID: 31869430.

ABSTRACT
In gestational diabetes mellitus (GDM), women are unable to compensate for the increased insulin resistance during pregnancy. Data are limited regarding the pharmacodynamic effects of metformin and glyburide during pregnancy. This study characterized insulin sensitivity (SI), β-cell responsivity, and disposition index (DI) in women with GDM utilizing a mixed-meal tolerance test (MMTT) before and during treatment with glyburide monotherapy (GLY, n = 38), metformin monotherapy (MET, n = 34), or GLY and MET combination therapy (COMBO; n = 36). GLY significantly decreased dynamic β-cell responsivity (31%). MET and COMBO significantly increased SI (121% and 83%, respectively). Whereas GLY, MET, and COMBO improved DI, metformin (MET and COMBO) demonstrated a larger increase in DI (P = 0.05) and a larger decrease in MMTT peak glucose concentrations (P = 0.03) than subjects taking only GLY. Maximizing SI with MET followed by increasing β-cell responsivity with GLY or supplementing with insulin might be a more optimal strategy for GDM management than monotherapy.

For full text, please **click here**.

Original Article:
Elizaldi SR, Verma A, Walter KA, Rolston M, Dinasarapu AR, Durbin-Johnson BP, Settles M, Kozlowski PA, **Raeman R**, Iyer SS. Rectal Microbiome Composition Correlates with Humoral Immunity to HIV-1 in Vaccinated Rhesus Macaques. mSphere. 2019 Dec 11;4(6). pii: e00824-19. doi: 10.1128/mSphere.00824-19. PubMed PMID: 31826975; PubMed Central PMCID: PMC6908426.

ABSTRACT

The microbiome is an integral and dynamic component of the host and is emerging as a critical determinant of immune responses; however, its influence on vaccine immunogenicity is largely not well understood. Here, we examined the pivotal relationship between the mucosal microbiome and vaccine-induced immune responses by assessing longitudinal changes in vaginal and rectal microbiome profiles after intradermal immunization with a human immunodeficiency virus type 1 (HIV-1) DNA vaccine in adult rhesus macaques that received two prior DNA primes. We report that both vaginal and rectal microbiomes were dominated by Firmicutes but were composed of distinct genera, denoting microbiome specialization across mucosal tissues. Following immunization, the vaginal microbiome was resilient, except for a transient decrease in Streptococcus In contrast, the rectal microbiome was far more responsive to vaccination, exhibiting an increase in the ratio of Firmicutes to Bacteroidetes Within Bacteroidetes, multiple genera were significantly decreased, including Prevotella, Alloprevotella, Bacteroides, Acetobacteroides, Falsiporphyromonas, and Anaerocella. Decreased abundance of Prevotella correlated with induction of gut-homing α4β7 + effector CD4 T cells. Prevotella abundance also negatively correlated with rectal HIV-1 specific IgG levels. While rectal Lactobacillus was unaltered following DNA vaccination, baseline Lactobacillus abundance showed strong associations with higher rectal HIV-1 gp140 IgA induced following a protein boost. Similarly, the abundance of Clostridium in cluster IV was associated with higher rectal HIV-1 gp140 IgG responses. Collectively, these data reveal that the temporal stability of bacterial communities following DNA immunization is site dependent and highlight the importance of host-microbiome interactions in shaping HIV-1 vaccine responses. Our findings have significant implications for microbial manipulation as a strategy to enhance

HIV vaccine-induced mucosal immunity.IMPORTANCE There is considerable effort directed toward evaluating HIV-1 vaccine platforms to select the most promising candidates for enhancing mucosal HIV-1 antibody. The most successful thus far, the RV144 trial provided partial protection due to waning HIV-1 antibody titers. In order to develop an effective HIV vaccine, it may therefore be important to understand how biological factors, such as the microbiome, modulate host immune responses. Furthermore, as intestinal microbiota antigens may generate antibodies cross-reactive to the HIV-1 envelope glycoprotein, understanding the relationship between gut microbiota composition and HIV-1 envelope antibody responses after vaccination is important. Here, we demonstrate for the first time in rhesus macaques that the rectal microbiome composition can influence HIV-1 vaccine immunogenicity, and we report temporal changes in the mucosal microbiome profile following HIV-1 vaccination. Our results could inform findings from the HIV Vaccine Trials Network (HVTN) vaccine studies and contribute to an understanding of how the microbiome influences HIV-1 antibody responses.

For full text, please **click here**.

Original Article:

Fisher JD, Balmert SC, Zhang W, Schweizer R, Schnider JT, Komatsu C, Dong L, Erbas VE, Unadkat JV, Aral AM, Acharya AP, Kulahci Y, Turnquist HR, **Thomson AW**, Solari MG, Gorantla VS, Little SR. Treg-inducing microparticles promote donor-specific tolerance in experimental vascularized composite allotransplantation. Proc Natl Acad Sci U S A. 2019 Dec 17;116(51):25784-25789. doi: 10.1073/pnas.1910701116. Epub 2019 Dec 2. PubMed PMID: 31792185; PubMed Central PMCID: PMC6925993.

ABSTRACT

For individuals who sustain devastating composite tissue loss, vascularized composite allotransplantation (VCA; e.g., hand and face transplantation) has the potential to restore appearance and function of the damaged tissues. As with solid organ transplantation, however, rejection must be controlled by multidrug systemic immunosuppression with substantial side effects. As an alternative therapeutic approach inspired by natural mechanisms the body uses to control inflammation, we developed a system to enrich regulatory T cells (Tregs) in an allograft. Microparticles were engineered to sustainably release TGF-β1, IL-2, and rapamycin, to induce Treg differentiation from naïve T cells. In a rat hindlimb VCA model, local administration of this Treg-inducing system, referred to as TRI-MP, prolonged allograft survival indefinitely without long-term systemic immunosuppression. TRI-MP treatment reduced expression of inflammatory mediators and enhanced expression of Treg-associated cytokines in allograft tissue. TRI-MP also enriched Treg and reduced inflammatory Th1 populations in allograft draining lymph nodes. This local immunotherapy imparted systemic donor-specific tolerance in otherwise immunocompetent rats, as evidenced by acceptance of secondary skin grafts from the hindlimb donor strain and rejection of skin grafts from a third-party donor strain. Ultimately, this therapeutic approach may reduce, or even eliminate, the need for systemic immunosuppression in VCA or solid organ transplantation.

For full text, please **click here**.

Review Article:

Argemi J and **Bataller R**. Hepatocyte-stellate cell synapse in alcohol-induced steatosis: another role for endocannabinoids. Nat Rev Gastroenterol Hepatol 2020. PMID 31686014.

ABSTRACT

A new study demonstrates a novel role for an endocannabinoid in promoting hepatocyte steatosis. The study describes a mode of bidirectional communication between the alcohol-injured hepatocyte and the glutamate-activated hepatic stellate cell. This intercellular communication represents a novel targetable pathogenic mechanism that could lead to new strategies to prevent fatty liver disease progression to cirrhosis.

Refers to Choi, W.-M. et al. Glutamate signaling in hepatic stellate cells drives alcoholic steatosis. Cell Metab. **https://doi.org/10.1016/j.cmet.2019.08.001** (2019).

For full text of review, please **click here**.

Original Article:

Artru F, Bou Saleh M, Maggiotto F, Lassailly G, Ningarhari M, Demaret J, Ntandja-Wandji LC, Pais de Barros JP, Labreuche J, Drumez E, Helou DG, Dharancy S, Gantier E, Périanin A, Chollet-Martin S, **Bataller R**, Mathurin P, Dubuquoy L, Louvet A. IL-33/ST2 pathway regulates neutrophil migration and predicts outcome in patients with severe alcoholic hepatitis. J Hepatol. 2020 Jan 15;S0168-8278(20)30008-8. doi: 10.1016/j.jhep.2019.12.017. [Epub ahead of print]. PMID: 31953139.

Background and aims: Severe alcoholic hepatitis (SAH) is associated with a high risk of infection. The interleukin-33 (IL33)/ST2 pathway is involved in sepsis control but data in alcohol-related liver disease (ALD) are lacking. We aimed to characterize the role of IL-33/ST2 in the neutrophils (PMNs) of patients with ALD and SAH.

Methods: Serum and circulating neutrophils were collected from patients with SAH, alcoholic cirrhosis (Cirrh) and healthy controls (Ctrl). We quantified the IL-33/ST2 pathway and CXCR2 at baseline and after exposure to IL-33. We also determined the migration capacity of PMN.

Results: The decoy receptor of IL-33 (sST2) was increased in SAH vs. Cirrh and Ctrl, demonstrating the defect in this pathway during ALD. The sST2 level was associated with response to treatment, 2-month survival, infection-free survival and probability of infection in SAH. Endotoxemia was weakly correlated with sST2. GRK2, a negative regulator of CXCR2, was overexpressed in SAH and Cirrh PMNs and was decreased by IL-33. CXCR2 levels on PMNs were lower in SAH vs. Cirrh and Ctrl. Treatment with IL-33 partially restored CXCR2 expression in SAH and Cirrh. PMN migration upon IL-8 was lower in SAH and Cirrh vs. Ctrl. Treatment with IL-33 partially restored migration in SAH and Cirrh. Interestingly, the migration capacity of PMNs and the response to IL-33 were enhanced in responders to corticosteroids (Lille<0.45) compared to non-responders.

Conclusion: The IL33/ST2 pathway is defective in SAH and predicts outcome. This defect is associated with decreased CXCR2 expression on the surface of PMNs and lower migration capacity, which can be corrected by IL-33, especially in patients responding to steroids. These results suggest a therapeutic potential in SAH and its infectious complications.

For full text, please **click here**.

Funding Opportunity

North America Corporate Grants

Gilead Sciences, Inc. / Gilead Sciences Pty Ltd

Our mailing address is:

Pittsburgh Liver Research Center

200 Lothrop St. | Pittsburgh, PA 15261